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Adhesion Molecule Expression in Acute and Chronic Exercise

*R. J. Shephard,[1,2,3] G. Gannon,[1] J. B. Hay,[4,5] and P. N. Shek[1,2,4]**

[1]Defence and Civil Institute of Environmental Medicine, Toronto; [2]Faculty of Physical Education and Health; [3]Department of Public Health Sciences; [4]Department of Laboratory Medicine and Pathobiology; and [5]Department of Immunology, Faculty of Medicine, University of Toronto, Ontario, Canada

* Address all correspondence to Dr P N Shek, Defence and Civil Institute of Environmental Medicine, 1133 Sheppard Avenue West, Toronto, Ontario M3M 3B9, Canada

Referee: Dr. Fabio Malavasi, Laboratory of Cell Biology, Department of Genetics, University of Torino, Torino, Italy

ABSTRACT: Adhesion molecules expressed on leukocytes and the vascular endothelial lining include the selectins, integrins, members of the immunoglobulin superfamily, and mucins. The changes in their expression that develop with acute and chronic exercise are briefly reviewed. Adhesion molecules are thought to modulate leukocyte trafficking, accounting for changes in the counts and possibly also the functional activity of various leukocyte subsets during and following an acute bout of physical activity. Some of the changes in the surface density of adhesion molecules can be explained through the action of epinephrine and other humoral factors on their expression, but an influence of sympathetic nerve terminals on cells sequestered in the spleen and liver, and an influx into the general circulation of leukocytes of differing phenotype also appear to be involved.

KEY WORDS: adhesion, selectins, integrins, immunoglobulins, mucins, catecholamines, cell trafficking, leukocytes

I. INTRODUCTION

Cellular adhesion molecules (CAMs) mediate cell–cell and cell–extracellular matrix interactions, influencing embryogenesis, angiogenesis, inflammation, wound repair, sepsis, tumor metastasis, transplant rejection, and atherosclerosis.[1] Within the immune system, they facilitate interactions between lymphocytes (for example, between the T and B cells,[2] and between NK cells and their targets). Adhesion processes transduce the signals that regulate leukocyte activation,[3] leukocyte growth, and differentiation. Adhesion molecules also provide the basis for the leukocyte trafficking and migration that modulate leukocyte counts during and following exercise;[4] they thus play a critical role in the homing of immune cells to specific tissues during inflammation and disease.[5,6]

Given the importance of adhesion molecules to many aspects of normal and pathological body function, the modifications of adhesion molecule expression and affinity induced by vigorous exercise and training[6] have considerable interest for the sports physician. This brief review summarizes the current classification of adhesion molecules, considers their respective functional roles and the overall process of lymphocyte trafficking, and looks at changes in the expression or affinity of adhesion molecules that develop during and following acute and chronic exercise.

II. STRUCTURE AND FUNCTION OF ADHESION MOLECULES

The current classification of adhesion molecules is based on similarities in structure

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and function.[7] The three most important categories are the selectins, integrins, and members of the immunoglobulin superfamily.[1,8] Mucins are a fourth family of cell receptors involved in cell–cell adhesion. The CD nomenclature, cell expression, and corresponding ligand molecules are summarized in Table 1.

A. Selectins

The selectins[9] are transmembrane glycoproteins found only on leukocytes (L-selectin), platelets (P-selectin), and vascular endothelium (E- and P-selectin). They play an important initial "tethering" role in the process of leukocyte–

TABLE 1
CD Nomenclature, Cellular Expression, and Ligands of Cell Adhesion Molecules

CAM family	CD nomenclature	Cell expression	Ligands
Selectins			
L-selectin	CD62L	L, G, M	CD34, GlyCAM-1, MAdCAM-1, CD62-P, -E
P-selectin	CD62P	P, E	PSGL-1, sLe^x, sLe^a, neutrophil L-selectin
E-selectin	CD62E	E	CLA, PSGL-1, $sLe^{x/a}$, neutrophil L-selectin
Integrins			
$\alpha_4\beta_1$ (VLA-4)	CD49d/CD29	L, M, Eos	Fibronectin, VCAM-1, MAdCAM-1 (weak)
$\alpha_L\beta_2$ (LFA-1)	CD11a/CD18	L, G, M, TM	ICAM-1, -2, -3
$\alpha_M\beta_2$ (Mac-1)	CD11b/CD18	L, G, M, TM	ICAM-1, FN, C3Bi
$\alpha_X\beta_2$	CD11c/CD18	M, G, L, DC	C3bi
$\alpha_4\beta_7$ (LPAM-1)	CD49d/CD?	Mem T, NK	FN, VCAM-1, MAdCAM-1
Ig-Superfamily			
CD4	CD4	T helper/inducer	
CD8	CD8	T cytotoxic	
LFA-2	CD2	L	LFA-3, CD48, CD59
LFA-3	CD58	L, M, G, E, TM	CD2
ICAM-1	CD54	Various cells	LFA-1, Mac-1
ICAM-2	CD102	L, M, DC, E	LFA-1
ICAM-3	CD50	L, G, M	LFA-1
VCAM-1	CD106	E, TM, DC, SC	VLA-4, LPAM-1
PECAM-1	CD31	E, P, L	LN, E, M, P, G
CD28	CD28		
CTLA-4	?		
B7	?		
Mucins			
MAdCAM-1	?	Mucosal HEV	LPAM-1, L-selectin, CD44, VLA-4, $\alpha_4\beta_7$
GlyCAM-1	?	PP, LN HEV	L-selectin
CD34	CD34	E	L-selectin
PSGL-1	?	L, M, G	P-, E-selectin
CD45	CD45	Ubiquitous	CD22

Note: Adapted from a classification of Dianzani and Malavasi.[9]
Abbreviations: **CLA,** cutaneous lymphocyte associated antigen; **DC,** dendritic cell; **E,** endothelium; **Eos,** eosinophil; **FN,** fibronectin, **G,** granulocyte; **GlyCAM,** glycosylation-dependent cell adhesion molecule, **HEV,** high endothelial venule; **ICAM,** intercellular adhesion molecule, **L,** lymphocyte; **M,** monocyte; **MAdCAM,** mucosal addressin cell adhesion molecule, **Mem,** memory; **NK,** natural killer cell, **P,** platelet; **PP,** Peyer's Patch; **PSGL-1,** P-selectin glycoprotein ligand, **SC,** bone marrow stromal cell; **TM,** tissue macrophage; **VCAM,** vascular cell adhesion molecule; **VLA,** very late activation antigen

endothelial cell adhesion associated with leukocyte trafficking and inflammation,[10] recognizing carbohydrate counterstructures on glycoproteins and glycolipids. Their long and flexible structure facilitates a rolling of leukocytes along the endothelial surface; conversely, the blocking of selectin-dependent pathways with fucoidin speeds the pulmonary capillary transit time by some 62%.[11]

The physical association of selectins with the TCR/CD3 complex on the surface of the T cell[12] and changes in the activation status of neutrophils on receptor ligation[13] suggest that these molecules also convey signals to some of the leukocyte subpopulation.

1. L-selectin

L-selectin is constitutively expressed on neutrophils, monocytes, B cells, and naive T cells;[14] expression by memory T cells and NK cells is more heterogeneous.[15,16] Splenic lymphocytes also express L-selectin at least weakly.[15] It mediates the initial attachment and slow rolling of lymphocytes along high endothelial venules within peripheral lymph nodes and Peyer's patches.[17]

Neutrophil L-selectin can be modified with sialyl Lewis^x; this process plays a specific targeting role in binding cells to E- and/or P-selectin on inflamed endothelium.[18] L-selectin levels on neutrophils decline as the cells age.[19] Proteolytic cleavage[20] sheds soluble (s) L-selectin into the plasma with activation of lymphocytes and neutrophils[21,22] and inflammation.[23] The soluble form of L-selectin retains its ligand-binding activity, so that in principle it could still regulate attachment of leukocytes to the vascular endothelium.[24] However, it is still debated how far this mechanism operates in practice.[25–28]

2. E-selectin

E-selectin is thought to recruit neutrophils and monocytes to sites of acute inflammation. It may also function as an adhesion molecule for skin-homing T memory cells that express the cutaneous lymphocyte antigen (CLA).[18] E-selectin is expressed transiently by vascular endothelial cells in response to stimulation by inflammatory mediators such as interleukin (IL)-1, tumor necrosis factor alpha (TNF-α), and bacterial lipopolysaccharide (LPS).[29,30] Expression peaks 2 to 4 hours after stimulation.[31,32]

3. P-selectin

P-selectin is constitutively synthesized by cells of the vascular endothelium. It is stored in granules known as Weibel-Palade bodies.[33] Within minutes of stimulation by inflammatory agents (for example, IL-1, TNF-α, LPS, histamine, complement fragments, or oxygen radicals), P-selectin is redistributed from the Weibel-Palade bodies to the surface of the vascular endothelium.[34] This allows binding by the counter-receptors on neutrophils, monocytes, and certain lymphocyte subsets at sites of tissue inflammation or injury.[35]

B. Integrins

The integrins are transmembrane glycoproteins found on various types of leukocyte, and on dendritic cells. They bind with proteins of the extracellular matrix (for example, laminin, collagen, and fibronectin) and with members of the immunoglobulin superfamily,[27,36] thus mediating both adhesion between cells and with extracellular proteins.[37,38] The β_1 integrins are also known as very late activation antigen (VLA) proteins. For example, VLA-4 (found on both resting and activated T and B lymphocytes) carries the α_4 (CD49d) chain. The β_2 integrins share a common β_2 (CD18) unit.

LFA-1 (CD11a/CD18), Mac-1 (CD11b/CD18), and VLA-4 are the most important integrins in the context of leukocyte/endothelial interactions.[30] Transformation of LFA-1 from the inactive to the active form can be induced by CD2/CD3, phorbol myristate acetate,[39,40] surface molecules such as CD31, cytokines such as IL-8, and chemotactic peptides such as fMLP.[30] An intracellular signaling cascade involves the cytoplasmic domain of the integrin, G proteins, phospholipids, and protein kinases.[41] Affinity is also influenced by changes in core temperature and

physical forces,[30] and can be up-regulated by Mg^{2+} and Mn^{2+}, and down-regulated by Ca^{2+}.[40-47]

Activation of LFA-1 causes leukocyte aggregation,[46,48] and this molecule is intimately involved in interactions between T and B cells.[49,50] Activation of the T cells up-regulates the affinity of LFA-1 for an adhesion molecule on the surface of the B cells (ICAM-1). Adhesion and interaction of the two cell types is then assured by up-regulation of other proteins (CD2 and CD8) on the surface of the T cell.[51,52]

VLA-4 recognizes and binds to VCAM-1 expressed on nonlymphoid endothelium.[45] It is also involved in the adhesion of leukocytes to cytokine-activated endothelial cells.[37,38]

C. Immunoglobulin Superfamily

Molecules of the immunoglobulin family are primarily ligands for integrins, playing a pivotal role in leukocyte–endothelial interactions and subsequent transendothelial migration through interactions between ICAM-1, CD54 and (ICAM)-2, CD102, and the integrins LFA-1 and Mac-1.[53] VCAM-1 contributes to this process, binding to VLA-4 integrins expressed by the leukocytes.[54] The immunoglobulin superfamily also contributes to T-cell activation and antigen recognition.[55] Intercellular adhesion molecules such as ICAM-1 can induce the transmission of signals between immune cells (for example, between antigen-presenting macrophages and lymphocytes), and can ensure a close contact between lymphocytes and tumor cells.

Two of the most important members of this grouping are ICAM-1, CD54, and VCAM-1, CD106. ICAM-1 is widely distributed, and is constitutively expressed on both resting endothelial cells and monocytes. It is dramatically up-regulated by stimulation from cytokines such as IL-1, TNF-α, and interferon.[56] VCAM-1 is found on endothelium, T memory cells, dendritic cells, and bone marrow stromal cells.

D. Mucins

Mucins are associated with either endothelium or leukocytes, and serve primarily as ligands for selectins.[57] Glycosylation-dependent cell adhesion molecule-1 (GlycCAM-1) is expressed almost exclusively on the high endothelial venules of peripheral and mesenteric lymph nodes,[58] and is a tissue-specific ligand for L-selectin. CD34 is also expressed on the vascular endothelium.[59] Mucosal addressin cell adhesion molecule (MAdCAM-1) also binds L-selectin, but it is an addressin-dependent cell adhesion molecule;[60,61] it is found primarily on the high endothelial venules of Peyer's Patches and mesenteric lymph nodes, and the lamina propria of the gut.[62] P-selectin glycoprotein ligand (PSGL)-1 is expressed by all leukocytes; it is a counter-receptor for P-selectin,[63,64] but it also binds E-selectin;[65] it is expressed by all leukocytes.

III. LEUKOCYTE TRAFFICKING

The ability of leukocytes to migrate between body tissue compartments is a central feature of both host defense and the inflammatory/remodeling processes that follow acute and chronic exercise. Neutrophils and monocytes follow a unidirectional path, moving from the blood stream into inflamed tissues. In contrast, most lymphocytes can migrate from the blood into the tissues, returning to the circulation via the lymphatic vessels.[66,67] We will summarize briefly the essentials of lymphocyte compartmentalization, routes of trafficking, and the role of adhesion molecules in controlling or directing this traffic.

A. Types of Lymphoid Tissue

The body contains primary, secondary, and tertiary lymphoid tissues. Primary lymphoid organs include the bone marrow and the thymus. Besides functioning as sites of hematopoiesis, these tissues are responsible for the negative selection of self-reactive B and T cells, and the positive selection of mature lymphocytes that are capable of mounting a normal immune response.[68] Secondary lymphoid structures include the spleen, peripheral lymph nodes, and mucosal associated lymphoid tissues (MALT). The spleen traps blood-borne antigens, and MALT structures collect antigens that have crossed the mucous linings of the digestive, res-

piratory, and urogenital tracts.[69–72] Tertiary lymphoid tissues include organs that have appreciable intravascular and parenchyma-associated lymphocyte populations (for example, the lungs, liver, gut, and kidneys).

B. Lymphocyte Distribution

The body contains some 500 to 1,000 × 10^9 lymphocytes, depending upon age.[73,74] Some 50% of this total are found in the lymph nodes and spleen.[75] At any given time, only 1 to 2 % of the total lymphocyte pool are circulating freely within the bloodstream,[73,74] and a significant proportion of the lymphocytes found within the spleen, lungs, liver, and kidneys are sequestered or intravascularly marginated cells. There are several different pools of lymphocytes to consider, in addition to the distribution patterns of subsets. From thoracic drainage studies, it has been determined that the continuously recirculating lymphocyte pool is about 10% of the total or 10 times that of the blood pool.[76]

The processes of delivery and migration of lymphocytes are tightly regulated, and normally the circulating numbers of the various lymphocyte subsets remain relatively constant.[77,78] However, changes in the properties of adhesion molecules can induce major transient alterations in total and differential counts, in response to exercise and other forms of stress.

C. Pathways of Lymphocyte Recirculation

On average, lymphocytes spend a few hours in the blood stream.[79,80] From labeled lymphocyte studies, it appears that blood lymphocytes turn over several times a day. However, the migratory potential of a substantial proportion of blood lymphocytes differs from that of lymph lymphocytes. Splenectomy may preferentially affect this blood pool. Although there is a large-scale lymphocyte traffic through high endothelial venules (HEV) of lymph nodes and through tertiary lymphoid tissues, there is a continuous traffic of lymphocytes (monocytes) through interstitial tissues and then into afferent lymphatics. These tissue lymphocytes migrate through the lymph nodes and into efferent lymph, but the monocytes terminate their migration in the nodes.

As they pass through the peripheral lymph nodes, inflamed skin, and mucosal lymphatic tissue, the lymphocytes enter specialized HEV.[81] These venules have a cuboidal-shaped endothelial lining that is quite distinct from the squamous endothelium found in the thymus, spleen, and bone marrow,[82] and is well-suited to the process of cell transmigration.[83] Some 25% of lymphocytes bind to the HEV endothelium and emigrate into the surrounding lymphoid tissue,[84] where they may be held or move back into the circulation via the efferent lymphatics.[85] The remaining lymphoid tissues have different mechanisms for the capture and emigration of lymphocytes.[86] In the pulmonary circulation, capillary sequestration predominates, but in the larger sinusoids and venules of the spleen, bone marrow and liver cells leave the axial stream of the blood and become loosely tethered to the endothelium. In most tissues, a proportion of these lymphocytes traverse the endothelium and are returned to the bloodstream via an afferent lymph–lymph node–efferent lymph pathway. In contrast to the T and B cells, natural killer (NK) cells do not appear to recirculate.[87,88] However, trafficking of NK cells from the circulation to the tissues has been demonstrated after the infusion of cortisol[89,90] and IL-6.[91]

The most potent cytokines that can cause extravasation of lymphocytes at a normally "low traffic" site (skin, bowel, synovium, periodontal tissues) are TNF-α and IFN-γ.[92–94] Many other cytokines do not promote lymphocyte extravasation. The enhanced expression of endothelial adhesion molecules is the most favored view regarding the mechanism of action of these cytokines.

Trafficking in any given tissue depends on mechanisms for the delivery, exit, migration, and passage of cells into and out of the lymphoid tissue.[77]

1. Delivery

The probability that a given leukocyte will be delivered to a specific tissue depends on the fraction of the total cardiac output that a given tissue receives. Thus, delivery is by far the great-

est to the lungs. Many more lymphocytes are also delivered to the liver, kidneys, spleen, and heart than to the lymph nodes. The latter receive only 1 to 2% of the resting cardiac output,[95] and an even smaller fraction of the circulating blood during vigorous exercise.

2. Migration Pathways

The output of lymphocytes from the thoracic duct (30×10^9 per day), together with the flow from other lymphatics (head and neck), is such that about 10 times the blood lymphocyte total reenters the blood, from lymph, each day; nevertheless, this accounts for only about 6% of the daily lymphocyte traffic.[87] Most lymphocytes must thus follow a migration pathway other than blood–tissue–lymph–thoracic duct.[96] Reinfusion of labeled lymphocytes shows the spleen,[97] lungs,[98] and liver[98] are predominant routes for sequestration of labeled cells. However, the phenomenon may be entirely intravascular and quite short-lived. When labeled lymphocytes are given several days to equilibrate and then monitored in blood and lymph, the concentrations of labeled cells falls by 50% every 16 days.[99]

At any one instant, the spleen contains some 14% of the total lymphocyte pool.[74] The importance of this organ is demonstrated by the effects of splenectomy. Removal of the spleen increases the mean residence time of lymphocytes within the blood,[100] impairs the lymphocytosis[101] but not necessarily the leukocytosis of exercise,[102] and alters the distribution of lymphocyte subsets.[103]

3. Steps in Migration

The first step in lymphocyte migration is adhesion of the cell to the vascular endothelium. In all secondary lymphoid organs except the spleen, adherence and transendothelial migration occur in HEV.[104] The binding sequence includes rolling, activation, firm attachment, and extravasation of the lymphocytes.[105,106]

Tethering, rolling, or primary adhesion[107] begins when cytokine messengers released by tissue inflammation or injury, particularly IL-1 and TNF-α, up-regulate the expression of adhesion molecules (predominantly selectins) on the leukocytes. Reaction between the selectins on the leukocytes and HEV mucins (addressins) such as GlyCAM-1, CD34, and/or MAdCAM-1 induces a slow rolling motion of leukocytes along the endothelium.[59,108,109] Some of the integrins, such as $\alpha_4\beta_1$ and $\alpha_4\beta_7$ can also mediate the rolling process.[110]

L-selectin and $\alpha_4\beta_1$, located on microvilli, allow a rapid and reversible attachment of lymphocytes to the HEV,[111] giving the cell time to sample the local endothelial environment for further triggering or activation signals.[112] The proinflammatory cytokines then interact with the appropriate G protein or tyrosine kinase,[113] triggering a lymphocyte receptor such as CD31 or the T-cell receptor,[114] and activating integrins and adhesion molecules of the Ig superfamily on lymphocytes and endothelial cells, respectively. Strong adhesion of the leukocytes to the vascular lining develops as integrins on the leukocytes (such as LFA-1, Mac-1, or VLA-4) bind to appropriate ligands in the endothelium (ICAM-1, ICAM-2, or VCAM-1).[115]

Finally, chemotactic stimuli encourage the leukocytes to migrate through the endothelium into the inflamed tissues. VLA proteins that can bind constituents of the extracellular matrix (collagen, fibronectin, and laminin) are involved in this step.[37,38] The process is accompanied by a release of the soluble product (sICAM-1) into the bloodstream.

4. Homing Mechanisms

Specific homing receptors on the lymphocytes and corresponding addressins on the endothelial cells direct individual subsets of lymphocytes to characteristic tissues.[17,105,116] Thus B and T cells show a preferential homing to Peyer's Patch HEV and peripheral lymph node HEV, respectively,[117] and a subset of the T cells homes to gut-associated lymphoid tissue.[118] Naive (CD45RA) and memory (CD45RO) T cells show distinct paths of recirculation (blood to lymph node and blood to tertiary lymphoid tissue, respectively).[119,120]

Memory develops through the up-regulation of specific cell adhesion molecules characteristic of the microenvironment where the T

cell or its progenitors first encountered its specific antigen.[121,122]

IV. EFFECTS OF EXERCISE

A. Leukocyte Counts

Sequestered cells can be mobilized rapidly during exercise, giving rise to a dramatic increase in circulating cell counts within the first minutes of exercise[123–125] and changes in the differential cell count[126] (Figure 1). Reinfusion of autologous, $DF^{32}P$-labeled granulocytes has demonstrated a recruitment of these cells from the marginated cell pool,[127] and the acute increases in other leukocyte subsets are also thought to arise primarily from a recruitment of cells normally sequestered in the various categories of lymphoid tissue.

Of the various types of lymphocyte, the B-cell count often shows no more than a small increase, but there are larger changes in T-cell count, and a dramatic two- to fivefold immediate increase in NK cell count.[128] A significant increase of NK cell count is induced by as little as 30 seconds of exercise at 100% of aerobic power, but if exercise is prolonged, there may be no further increase in NK count after 30 to 60 minutes of activity; indeed, with very prolonged exercise, the NK cell count may even return toward normal resting levels.[129] The threshold intensity of effort needed to increase the circulating NK cell count seems to be about 50% of aerobic power. Above this threshold, the higher the intensity of exercise of a given duration, the larger the increase in circulating NK cell count[128,129] (Figure 2).

Following exercise, the NK cell count may drop below resting levels. A minimum is usually reached 30 to 180 minutes postexercise, with recovery 2 to 24 hours postexercise, although occasionally the suppression of circulating NK count may persist for as long as 7 days.[129]

B. Leukocyte Adhesiveness

Available information on the impact of acute exercise on leukocyte and endothelial adhesion is summarized in Table 2.

1. Neutrophils

Neutrophil adhesion depends primarily on expression of the integrins CD11a/CD18 and CD11b/CD18.[45] Some early reports suggested that neutrophils showed no change in their capacity for adherence to organisms or endothelium immediately after a bout of exercise at 50% of aerobic power[130] or exercise to exhaustion.[131] Lewicki and associates[132] found no effect of a bout of maximal exercise in 19 untrained young men, but in 20 conditioned cyclists there was a decrease in adherence and neutrophil bactericidal activity.

A change in adherence might be anticipated, at least in the period following vigorous exercise, because the neutrophils that are released from bone marrow in response to such a stimulus express high levels of L-selectin, and low levels of CD18.[133,134] In discussing changes in adherence, it is thus important to distinguish the immediate and late neutrophil responses to exercise. Surface densities of CD11b and CD11c remained unchanged during the immediate and delayed neutrocytosis induced by an hour of exercise at 60% of maximal oxygen intake.[135] However, the expression of L-selectin was decreased during the early neutrocytosis, but the surface density of CD62L neutrophils increased during the secondary neutrocytosis, probably due to a selective influx of $CD62L^{high}$ neutrophils from the bone marrow.[135] Gabriel[30] found increases of CD11b and CD18 at the end of exercise to exhaustion at 110% of anaerobic threshold; but 2 and 6 hours postexercise, the receptor densities for both CD11a and CD11b were lower than on control days.

The intensity of effort seems an important determinant of response. Jordan and associates[136,137] found an 11% increase of CD11b expression immediately after a progressive treadmill test and a 105% increase after a marathon run, but no change after a moderate 3-hour run.

Other investigators have found an increased density of L-selectin in $CD62L^+$-positive cells but no change in the proportion of neutrophils expressing $CD62L^+$ in women immediately after they had performed six sets of 10-repetition maximum squats over 15 minutes;[138,139] an increased CD11b expression 6 and 24 hours following 16

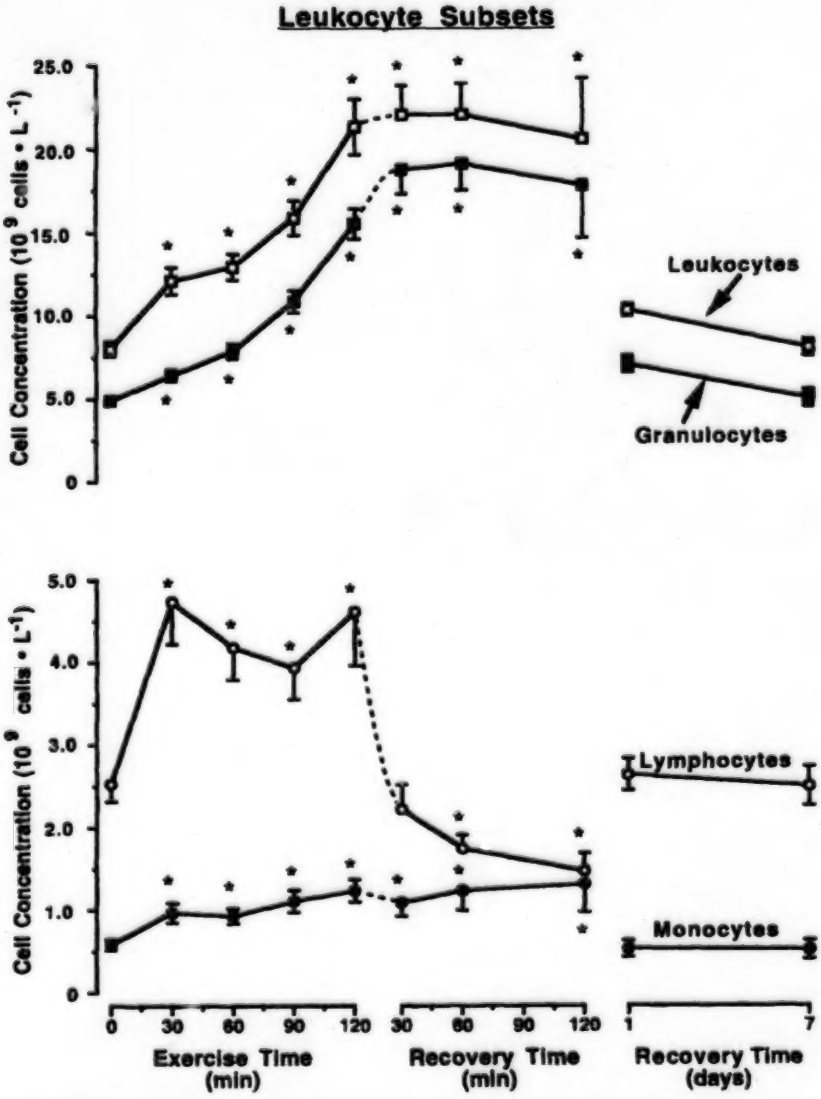

FIGURE 1. Changes in circulating leukocyte subset counts induced by a bout of treadmill exercise for 2 hours at 65% of aerobic power. Each astensk denotes a significant difference ($p < 0.05$) between the mean value and that at time zero (based on the data in Reference 126).

one-minute treadmill runs to exhaustion;[140] and increased CD11b expression after a marathon race,[141] but not a moderate 3-hour run.[141] Plasma levels of soluble L-selectin were not increased following 40 km of relay running during a 24-hour interval.[142]

Where there is a change in receptor density, possible explanations include a mobilization of

bone marrow neutrophils with low integrin densities, a shedding or internalization of receptors, or a blockade of receptors by soluble factors (for instance, complement fragments or fibrinogen).[30] In the case of CD11a, proteolytic cleavage is theoretically possible, but shedding of the receptor into the plasma has yet to be described. Internalization is also unlikely, because no intracellular storage sites have been found.[143] However, internal stores of CD11b are modulated by a variety of soluble factors, including calcium ionophore and TNF-α.[45]

Pizza and colleagues[144] had subjects perform two bouts of eccentric exercise at intervals of 3 weeks; both tests increased neutrophil expression of CD11b and CD64, but 72 hours postexercise the expression of CD11b (2.7-fold) and CD64 (1.4-fold) was higher in the first than in the second trial, suggesting that repetition of the exercise led to a lesser activation of neutrophils.

2. Monocytes and Macrophages

It has been inferred from the phagocytic process in peritoneal cells that exercise does not change adhesion in macrophages.[145–148] However, peritoneal macrophages from young guinea pigs

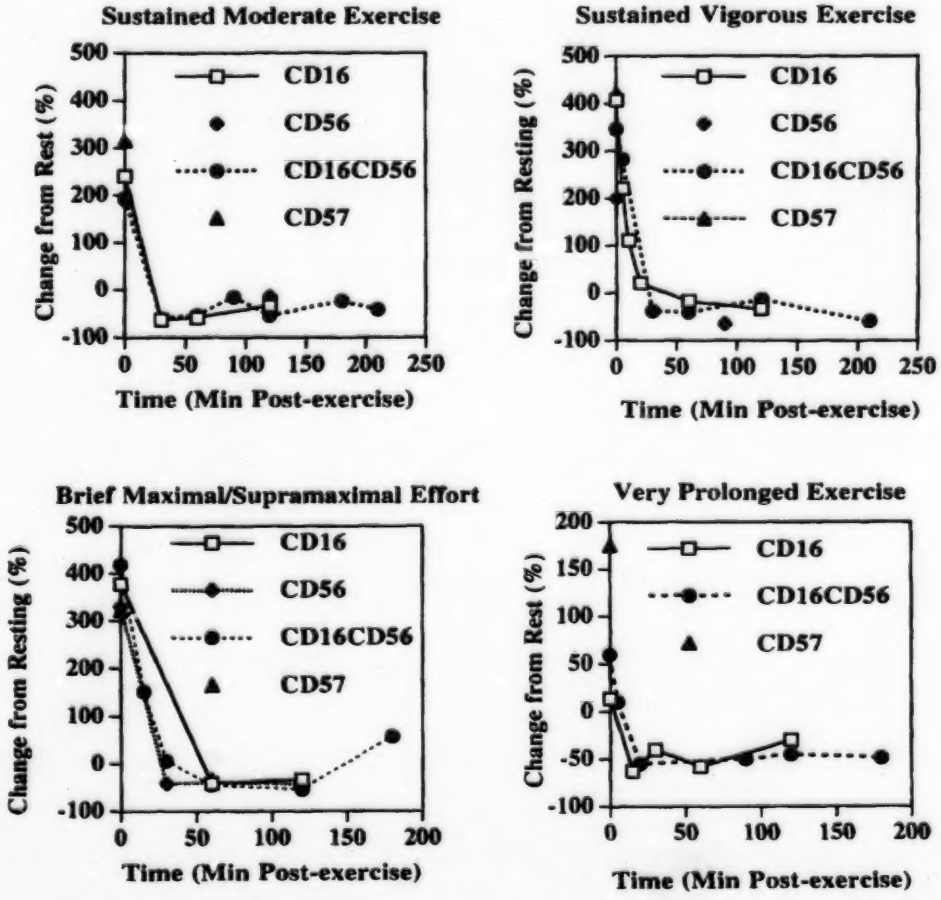

FIGURE 2. The relationship between the intensity of exercise and changes in NK cell count following a bout of exercise (based on a meta-analysis from Reference 129)

TABLE 2
The Impact of Acute Exercise on the Expression of Adhesion Molecules on Leukocytes and Endothelial Cells

Type of exercise	Response	Refs.
Neutrophils		
Cycle ergometer exercise at 50% of aerobic power	No increase in neutrophil adherence against *Candida albicans* immediately postexercise; some increase in attachment after 15 min incubation (not seen 15 min postexercise)	130
Exhausting running exercise	No change in adherence to endothelium postexercise	131
Maximal exercise	Decreased adherence in 20 trained cyclists; no change in untrained subjects	132
60 min exercise at 60% of aerobic power	Early decrease in surface density of CD62L Increase in CD62L during secondary neutrocytosis	135
Exercise to exhaustion at 110% of anaerobic threshold	Increase of CD11b and CD18 at end of exercise, decrease of receptor density for CD11a and CD11b 2 and 6 h postexercise	149
Progressive treadmill test	CD11b 11% increase postexercise	136
Marathon run	CD11b 105% increase postexercise	136
Moderate 3 h run	No change in adhesion receptors	136
Six sets of 10 rep. maximal squats (women)	No change in proportion of $CD62L^+$ cells Increased density on positive cells	139
Sixteen 1 min runs to exhaustion	Increased CD11b expression at 6 and 24 h	140
Marathon run	Increased CD11b expression	141
Moderate 3 h run	No change in adhesion molecules	141
Two bouts of eccentric exercise separated by 3 weeks	Both show increased expression of CD11b postexercise—greater increase in first trial	144
40 km of relay running over 24 h	No increase in serum soluble selectin	142
Monocytes and macrophages		
BALB mice swim to exhaustion	No change in macrophage adherence to substrate	145
BALB mice swim 90 min daily for 20 days	No change in macrophage adherence capacity but increased spontaneous attachment to *Candida albicans*	146
Swim to exhaustion (young guinea pigs)	Peritoneal macrophage adherence to tissue substrate increased immediately, 40 min and 24 h postexercise	148
Swim to exhaustion (old guinea pigs)	Pentoneal macrophages show no change in adherence immediately postexercise, decreased 24 h postexercise	148
One min all-out exercise	Increased proportion of mature ($CD16^+$) LFA-1 high positive monocytes at expense of regular (CD16-) low LFA-1 positive	149
Exercise to exhaustion in 24 min	As above	148
Exercise to exhaustion in 87 min	Similar increase in regular and mature monocytes	148
100 km run	Increase of regular, decrease of mature monocytes	148
3 h run at 50 to 60% max velocity	Decreased monocyte expression of CD11a, CD11c, CD29, CD49	136
Maximal treadmill test	Increased CD11b expression, no change CD18	150
Marathon run	As above	150
3 h run at 50 to 60% max velocity	No change in CD11b or CD18	150

TABLE 2 (continued)

Type of exercise	Response	Refs.
Eccentric exercise	Increased expression CD11b, CD62L 6 to 48 h postexercise	152
Two bouts eccentric exercise (25 forced lengthening contractions of forearm flexors)	CD11b increased in both tests, peak 24 h postexercise, increase of CD18 and CD64 72 and 96 h postexercise greater in first test	144
Lymphocytes and NK cells		
60 min aerobic exercise at 60% aerobic power	Increase in lymphocyte subsets positively correlated with initial expression of CD11a	154
3 h of exercise at 50 to 60% max velocity	Decreased lymphocyte expression of CD11a and CD18	136
100 km run	Decrease in circulating numbers of T and NK cells with high surface density CD11a	149
Endothelium		
All-out cycle ergometry	No change in serum sE-selectin, sVCAM-1, or sICAM-1	157
60 min of exercise at 60% of maximal intensity	As above	157

swum to exhaustion show an increased adherence to tissue substrate immediately, 40 minutes and 24 hours postexercise.[147,148] In humans, a brief bout of anaerobic exercise increased the proportion of circulating mature ($CD14^+CD16^+$) LFA-1 high positive monocytes at the expense of regular low LFA-1 positive monocytes ($CD14^+CD16^-$); the reverse was true for a prolonged (100 km) ultraendurance run.[149] Likewise, the monocyte expression of CD11a, CD11c, CD29, and CD49 was decreased following a 3-hour bout of submaximal exercise.[136,137] The expression of CD11b was increased after a maximal treadmill test and a marathon run, but not after the moderate 3-hour run; CD18 expression was unchanged after any type of exercise.[150] Differential homing is probably involved, because in comparison with mature monocytes, regular monocytes express less CD11a and CD18, but more CD11b.[6,151] A suggested mechanism is a change in avidity of the adhesion molecules associated with ar increase of body temperature and the secretion of proinflammatory cytokines such as TNF-α.[106]

The monocyte expression of CD11b and CD62L was increased following eccentric exercise.[152] When two bouts of eccentric arm exercise were performed with an intertest interval of 3 weeks, the monocyte expression of CD11b increased in both instances, to peak 24 hours postexercise; however, CD18 and CD64 was 1.3 times higher for the first than for the second test 72 and 96 hours after exercise.[144,153]

3. Lymphocytes and NK Cells

Selective changes occur in the circulating numbers and characteristics of human lymphocytes. In response to a 1-hour bout of aerobic exercise at 60 to 65% of maximal oxygen intake, $CD4^+$ cell counts increased 23%, with 80% of these cells having a memory ($CD45\ RO^+$) phenotype. A 44% increase in the number of circulating $CD8^{bri+}$ cells was attributable to much closer proportions of naive (43%) and memory (57%) cells.[154]

The majority of lymphocytes that are mobilized, in response to a prolonged bout of aerobic[5,135] or resistance exercise,[155] express high levels of CD11a and low levels of CD62L.[135] Moreover, increases in individual lymphocyte subsets ($CD56^+$ [330%], $CD8^{bri+}$ [105%] and $CD4^+$ [30%]) are positively correlated with im-

tial resting levels of CD11a ($CD56^+$ 270 MFU; $CD8^{bs+}$ 176 MFU; $CD4^+$ 107 MFU).[154,156] $CD8^+$ $CD11a^{high+}$ lymphocytes are either memory T cells or NK cells weakly coexpressing CD8.[30] Because memory T cells with high levels of CD11a expression are the predominant phenotype within the marginal lymphocyte pool, it is not surprising that the majority of the T cells mobilized to the blood during heavy physical exercise are of the memory phenotype.

Jordan and associates[136,137] reported a decreased lymphocyte expression of CD11a and CD18 after 3 hours of submaximal exercise. Likewise, following a very prolonged bout of endurance exercise (a 100 km run), there was a decrease in the circulating numbers of T cells and NK cells with a high surface density of CD11a.[149] Internalization of the receptor is not thought possible for this decrease.[143] There may be binding of the receptor by some soluble factor, or a shedding of the receptor, but the most likely explanation seems a selective outward migration of cells with a high expression of CD11a.[30]

4. Endothelium

Neither all-out cycle ergometry nor an hour of endurance exercise at 60% of maximal work intensity induced any substantial change in serum levels of the soluble adhesion molecules sE-selectin, sVCAM-1, and sICAM-1.[157]

C. Mechanisms of Change

1. Mechanical Effects

Early investigators suggested that the leukocyte mobilization associated with exercise was due to a redistribution of blood flow, mechanical shear factors associated with an increase of cardiac output,[158–161] or activation-induced changes in cell deformability and thus ease of trapping in the pulmonary circulation.[161] However, it is hard to see why such mechanisms should have a threshold as high as 50% of aerobic power, and why the mobilization of leukocytes should wane with very prolonged activity or repetition of an exercise bout. Changes in differential cell counts also seem difficult to explain in purely mechanical terms.

2. Alterations in Adhesion Processes

The most widely accepted hypothesis today is that the trafficking of leukocytes is modulated by changes in the affinity or surface density of adhesion molecules, exercise-induced hormonal responses (particularly the secretion of catecholamines) providing the trigger to alterations in the avidity of adhesion molecules. Evidence in support of this hypothesis is drawn from the parallel between catecholamine levels and cellular changes, the mimicking of changes by the infusion of catecholamines, and the blocking of response by catecholamine antagonists. However, the proof is not categoric, because changes in catecholamine levels not only modify the expression of adhesion molecules, but also modify the circulatory response to exercise. Further, exercise-induced changes in other soluble factors, such as $Mg2^+/Ca2^+$ balance and inflammation-related cytokines may contribute to the observed response.

In the absence of shedding or internalization of the adhesion molecules, changes in the per-cell expression of adhesion molecules may reflect the mobilization of sequestered cells with a differing phenotype, altered patterns of leukocyte trafficking, or selective apoptosis.

3. Role of Catecholamines

The beta-receptors on lymphocytes are linked intracellularly to the adenyl cyclase system, and thus can generate cAMP as a second messenger.[162] Catecholamine-induced changes in configuration of portions of the selectin molecule (the EGF-like and SCR domains) can modify affinity of CD62L for its carbohydrate ligands.[163,164] A burst of exercise leads to major increases in blood concentrations of norepinephrine[165,166] and (with more vigorous activity) of epinephrine;[167] circulating concentrations of epinephrine increase in exponential fashion at exercise intensities above 70% of maximal aerobic power. The various leukocytes all carry cate-

cholamine receptors. The surface density of the catecholamine receptors is greatest for NK cells, less for B and $CD8^+$ cells, and least for $CD4^+$ cells.[168–170] In keeping with this gradation, exercise has a much greater impact on NK than on B- and T-cell counts;[171,172] the mobilization of B cells is disadvantaged not only by a lower catecholamine receptor density, but also by the lack of a second messenger system.

The catecholamine receptor density is increased by a bout of exercise,[173–178] several fold on NK cells,[162] 120% on $CD4^+$ cells, and 80% on $CD8^+$ cells.[179] There are corresponding increases of intracellular cAMP production.[180] Possibly, alterations in the sensitivity of the β-receptors play an important role in modulating demargination and subsequent readhesion of leukocytes during and following an acute bout of exercise.[170,181] Recent observations show that the normal exercise-induced shedding of the immunoglobulin ligand ICAM-1 is blocked by administration of either propranolol or metoprolol;[182] however, exercise does not modify serum levels of soluble E-selectin.

Circulating levels of catecholamines drop rapidly following exercise, and the density of catecholamine receptors returns to resting[173] or even less than baseline levels[183,184] within an hour of ceasing exercise, thus offering an explanation of the rapid reversal in circulating lymphocyte counts following exercise. In contrast to the effects of an acute burst of exercise, habitual physical activity leads to as much as a 60% decrease in the resting surface density of the β-receptors.[185,186]

Although a short burst of activity up-regulates catecholamine receptors, the prolonged infusion of epinephrine down-regulates β-receptors, both in vitro[187,188] and in vivo.[189] Again in keeping with these changes, NK cell counts decline from their initial peak during very prolonged bouts of exercise.[129]

4. Epinephrine or Norepinephrine?

Certain features of the leukocyte response to exercise can be mimicked, at least in part, by infusion of appropriate doses of epinephrine[141,168,190,191] or norepinephrine,[192] although exercise induces a larger increase in neutrophil count than does a corresponding plasma concentration of epinephrine.[141,193]

The exercise-induced changes in cell counts are correlated with changes in plasma concentrations of norepinephrine (in moderate exercise);[194–198] and epinephrine (in very vigorous, exhausting exercise).[141,194,199–201] Parts of the exercise response can be eliminated by administration of a nonspecific β-blocker,[202] although the leukocytosis is reduced rather than abolished by such treatment,[159] and exercise-induced changes in NK count and activity remain unaffected.[203] Metoprolol (a selective β-1 blocker) does not change the exercise-induced response,[170] suggesting that a β-2 adrenergic reaction is responsible.

Interactions between catecholamines, β-2 receptors, and adhesion molecules thus seem able to explain much of the observed exercise-induced changes in T-cell counts. β-Agonists can also cause a detachment of NK cells from cultured endothelium in vitro,[127] and decrease the adhesion of neutrophils to nylon fibers.[204] However, the β-2 receptors are much more sensitive to epinephrine than to norepinephrine, and the doses of hormone needed to detach NK cells from the endothelium are much larger for norepinephrine than for epinephrine.[205] Norepinephrine probably acts largely via nerve terminals in the lymph nodes or spleen.[178,206,207] Splenectomy or drainage of the thoracic duct eliminates the leukocyte response to infusion of norepinephrine,[208] and the exercise-induced increase of NK cell count is seen in paraplegia but not in quadriplegia,[209] supporting the hypothesis of an action via sympathetic nerve terminals. Attempts to explain B-cell trafficking in terms of alterations in expression of LFA-1 have also been unsuccessful,[5] perhaps because of lack of an appropriate second messenger system in these cells.

5. Cytokine and Hormonal Involvement

Various proinflammatory cytokines released during exercise (particularly IL-2, IL-6, and IL-12) can all up-regulate adhesion molecules on the surface of the NK cells,[210,211] and may thus

play a role in modulating NK cell function during physical activity that is sufficiently vigorous to cause a subclinical inflammatory response.

Hormonal modulation of adhesion molecules may also play a role, particularly in the differential loss of activated NK cells from the circulation following physical activity.[212]

6. Implications for Cell Trafficking

Although catecholamine levels are likely to remain high and even to increase during prolonged exercise, the β-adrenoceptor expression of lymphocytes is attenuated during the final hour of a 3-hour run.[213] This might allow an up-regulation of cellular adhesion molecules, encouraging a progressive remargination of NK and T cells as exercise continues. Increasing plasma levels of cortisol[214] and IL-6[215,216] may also encourage a migration of neutrophils from bone marrow into the circulation and NK cells out of the circulation.

Following exercise, a remargination of leukocytes is favored by a decrease of shear stress, the short half-life of catecholamines, and a resulting up-regulation of adhesion molecules. In accordance with this scenario, the circulating numbers of NK cells fall rapidly in the first 30 minutes following an acute bout of exercise, but counts for neutrophils, eosinophils, and B and T lymphocytes tend to increase during the first 15 minutes postexercise.

V. EFFECTS OF TRAINING

There has been relatively little study of the changes in adhesion processes that result from training. A cross-sectional comparison[132] noted that whereas trained subjects showed a decreased adherence of neutrophils and monocytes in response to an acute bout of physical activity, sedentary individuals did not show such a response. Likewise, a cross-sectional comparison between sedentary men and male triathletes showed lower CD11a and CD18 monocyte receptor densities in the triathletes.[217]

The attachment capacity of macrophages of mice trained by swimming 90 minutes daily for 20 days was not increased, although spontaneous attachment of the macrophages to *Candida albicans* was increased.[146] A longitudinal study of track runners[218] found that the proportion of monocytes expressing ICAM-1 increased from the endurance phase of training through 8 weeks of sprint/strength training to competition, with an associated increase in the number of circulating monocytes; this was interpreted as evidence of activation of the monocyte/macrophage system. At the end of the endurance training phase, there was also an increase in serum levels of sICAM-1.[218] Because ICAM-1 is a receptor for some of the rhinoviruses that cause the common cold, this change could enhance the individual's resistance to upper respiratory infection.[219]

VI. FUTURE RESEARCH

Currently, there is only limited and conflicting information on changes in the expression of adhesion molecules during acute and chronic exercise, and the impact of these changes on leukocyte trafficking. Future research needs to define the initial state of training of subjects; the type, intensity, and duration of the exercise performed; the timing of blood sampling relative to exercise bouts; and the impact of repeated bouts of exercise on both resting status and the acute response to exercise. There is also a need to distinguish changes in the proportion of leukocytes carrying a given adhesion marker from changes in the per-cell affinity and surface density of that marker. If an exercise-induced change is observed, it remains to be determined whether this is due to a change in the characteristics of cells initially within the circulation, or whether it reflects the entry of a new and different cell population from some source outside the normal circulation. In the future, it will be feasible to track labeled leukocytes in humans and even use imaging techniques to thereby define distribution patterns in several compartments, in addition to venous blood.

Given the number and complexity of the various adhesion molecules, there is a need to explore whether any observed changes have practical consequences in terms of margination of cells and effectiveness of the leukocytes in

mounting a response against microorganisms. Finally, although there are persuasive arguments that catecholamines play a role in modulating the expression and action of adhesion molecules, various discrepancies in the β-receptor hypothesis such as the failure of catecholamines to induce a typical neutrocytosis and the relationship of NK cells to norepinephrine rather than epinephrine remain to be resolved.

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514212